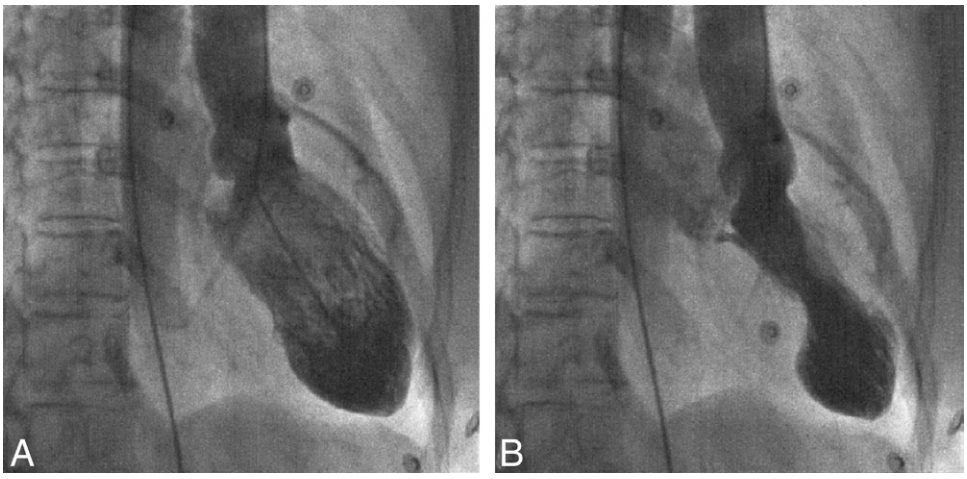

Figure 2 **Contrast Left Ventriculography in the Right Anterior Oblique Projection**

The left ventriculogram at end-diastole **(A)** and end-systole **(B)**, showing apical ballooning and basal hyperkinesis.

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Letters to the Editor

Cardiovascular Mortality in High-Risk Patients and T-786C Polymorphism in Promoter Region of the Endothelial Nitric Oxide Synthase Gene

Rossi et al. (1) reported very interesting and intriguing results of the first prospective study examining the possible effects of 2 single nucleotide polymorphisms (SNP) in the endothelial nitric oxide synthase (eNOS) gene (the T-786C SNP in the promoter region, and the G894T SNP in exon 7) on cardiovascular mortality among high-risk patients. Although no significant effects were found for the G894T SNP, more cardiovascular deaths were found when individuals with TT genotype for the T-786C SNP were compared with CC + CT individuals (1). The significant effect of T-786C SNP on cardiovascular mortality persisted even after many confounding factors were taken into consideration. However, a significant number of individuals (32%) were on lipid-lowering therapy at recruitment (1), and it is probable that an increased proportion of these subjects may have received statins thereafter.

Interestingly, although the T-786C SNP apparently does not significantly affect nitric oxide (NO) availability (2,3), it may modulate the responses to statins. In this regard, we have recently reported that treatment with atorvastatin significantly increased NO availability (measured as whole blood nitrite) in CC individuals, but not in TT individuals (4), thus confirming previous findings suggesting that statins may produce stronger effects on NO availability in CC individuals compared with TT individuals (5). In addition, atorvastatin significantly reduced the concentrations of inflammatory markers in subjects with CC (but not TT) genotype (6). Although these findings derive from studies that included healthy individuals, they suggest that statins may significantly modify the cardiovascular risk associated with the T-786C SNP. Indeed, it is possible that treatment with statins counteracts the effects associated with the T-786C SNP (4), thus leading to apparently paradoxical results such as those reported by Rossi et al. (1).

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Effects of Endothelial Nitric Oxide Synthase Gene Polymorphisms on Oxidative Stress, Inflammatory Status, and Coronary Atherosclerosis: An Example of a Transient Phenotype

In their recent study, Rossi et al. (1) showed that the T786C polymorphism on the promoter region of the endothelial nitric oxide synthase (eNOS) gene modifies redox-sensitive inflammatory pathways, and may be a predictor for clinical outcome in high-risk patients with coronary atherosclerosis. Although this polymorphism was found to be in linkage disequilibrium with the functional polymorphism G894T ($D' = 0.3$), the latter had no predictive value in this cohort, despite the results of a large meta-analysis suggesting the opposite (2). However, the observation that the 894T/786T haplotype leads to a worse cardiovascular death-free survival supports the hypothesis of a more complex association between these polymorphisms and eNOS function.

We have recently shown (3) that the presence of the 894T allele is associated with higher levels of oxidized low-density lipoprotein and proinflammatory cytokines only under conditions of "biological stress," such as during the acute phase of myocardial infarction, an effect not observed in the same subjects 1 year after the event, or in healthy individuals. Moreover, the 894T allele seems to be associated with impaired endothelial function in high-risk patients (4) and in healthy smokers (5), but not in healthy, low-risk individuals (5).

In the present study, Rossi et al. (1) actually introduce the hypothesis that the previously observed transient effect of the 894T allele on oxidative stress, inflammatory process, and endothelial function (3–5) could actually be due to its linkage disequilibrium with the 786T allele (which has been suggested to modify eNOS expression). However, this could be due to the complex interaction of both polymorphisms constituting the 894T/786T haplotype. The combination of low eNOS expression (induced by the 786T allele) and increased susceptibility of eNOS to proteolytic cleavage (induced by the 894T allele) (6) could lead to a combined effect on the associated phenotype of nitric oxide bioavailability, and the subsequent alterations of oxidative stress and inflammatory status. Therefore, further molecular studies are required to explore the transient behavior of eNOS genotypes/haplotypes, leading to a different phenotype, depending on the underlying disease state.

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Reply

To explain our (1) intriguing results on the effects of the T-786C (in the promoter) and the G894T (in exon 7) single nucleotide polymorphisms (SNP) of the endothelial nitric oxide (NO) synthase (eNOS)